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NEPHROLOGY FORUM

Hospital-associated hyponatremia

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Case presentation

Patient 1. An 18-year-old woman with cystic fibrosis was admitted to the hospital for evaluation of shortness of breath and a productive cough of one week duration. She had required hospitalization for pneumonia at ages 12 and 16 and again 6 months prior to the present admission. Fat malabsorption (30–50 g/day) and an elevated sweat chloride concentration had been documented. Medications at the time of admission included trimethoprim-sulfamethoxazole, one tablet twice daily; theophylline; and a pancreatic enzyme preparation.

Weight was 37 kg; temperature, 37°C; respiratory rate, 20/min; blood pressure, 104/76 mm Hg supine and 102/64 mm Hg upright. Pertinent physical findings included: clubbing of finger nails; diffuse coarse rales, rhonchi, and wheezes throughout the chest; and moist mucous membranes. There was no cyanosis or edema and skin turgor was normal. Laboratory data revealed: hemoglobin, 12.5 g/dl; white blood cell count, 15,000/mm³ (80% neutrophils, 4% bands, 13% lymphocytes); normal prothrombin time and PTT; albumin, 2.7 g/dl; BUN and creatinine, 6 and 0.5 mg/dl, respectively; and glucose, 96 mg/dl. Serum electrolytes were: sodium, 136; potassium, 3.5; chloride, 96; and total CO_2, 28 mEq/liter. Arterial blood gas measurements, obtained while the patient was breathing 4 liters of oxygen by nasal prongs, revealed a PO_2 of 67 mm Hg, a PCO_2 of 40 mm Hg, and a pH of 7.50. Chest x-ray disclosed bibasilar and right middle lobe infiltrates. Sputum culture grew large numbers of *Staphylococcus aureus* and pseudomonas species. The patient was treated with gentamicin, carbenicillin, and intravenous hypotonic fluids. Postural drainage also was employed. Two days later the serum sodium was 129; potassium, 3.5; chloride, 93; and total CO_2, 27 mEq/liter. Random urinary sodium was 74 mEq/liter and urine osmolality was 500 mOsm/kg H_2O. The patient was enrolled in a research protocol for elucidating the pathophysiology of hyponatremia. The following hormone measurements were obtained while she was supine: norepinephrine, 469 pg/ml; epinephrine, 190 pg/ml; plasma renin activity, 2.1 ng/ml/hr; plasma aldosterone, 4.3 ng/dl; and plasma arginine vasopressin, 2.1 pg/ml. Two liters of normal saline were administered, but neither body weight nor serum sodium concentration changed. The patient's course was complicated by a pneumothorax that required chest tube drainage. She was discharged 25 days after admission. At that time the serum sodium was 135; potassium, 3.9; chloride, 96; and total CO_2, 31 mEq/liter.

Patient 2. A 54-year-old woman was admitted to the hospital for elective repair of a Nisson fundal plication that had been performed because of severe reflux esophagitis. Physical examination was unremarkable. Preoperative laboratory data revealed: a normal complete blood count; serum creatinine, 1.1 mg/dl; and glucose, 88 mg/dl. Serum electrolytes were: sodium, 141; potassium, 4.1; chloride, 100; and total CO_2, 25 mEq/liter. The operative procedure was uncomplicated. On the first postoperative day, serum electrolytes were: sodium, 129; potassium, 3.5; chloride, 94; and total CO_2, 24 mEq/liter. Serum creatinine was 0.8 mg/dl; glucose, 108 mg/dl; random urinary sodium, 58 mEq/liter; and urine osmolality 450 mOsm/kg H_2O. The patient was asymptomatic. She had received 9000 ml of hypotonic fluid (0.45% and 0.2% saline) and had a urinary output of approximately 4 liters. Plasma arginine vasopressin was 1.8 pg/ml. Hypotonic fluid administration was discontinued and the patient's serum sodium concentration rose to 140 mEq/liter over the next 3 days.

Discussion

DR. ROBERT J. ANDERSON (*Head of Medical Service, Veterans Administration Hospital, and Professor of Medicine, University of Colorado Health Sciences Center, Denver, Colorado*): Hyponatremia is a common occurrence in hospitalized patients. In 1968, Owen and Campbell published frequency distribution curves that showed mean plasma sodium and chloride concentrations 5 to 6 mEq/liter lower in hospitalized patients than in healthy outpatient control subjects [1] (Fig. 1). Mean plasma potassium and bicarbonate concentrations were comparable in the two groups. In a recent prospective study, we found daily incidence and prevalence rates of hyponatremia (serum sodium, <130 mEq/liter) of approximately 1% and 2.5% respectively, in hospitalized patients on general, medical-surgical wards [2]. Hyponatremia not only is a frequent occurrence, it also is associated with substantial morbidity and mortality [3–6]. Because I believe that an understanding of the pathophysiology of hospital-associated hyponatremia can lead to its preven-

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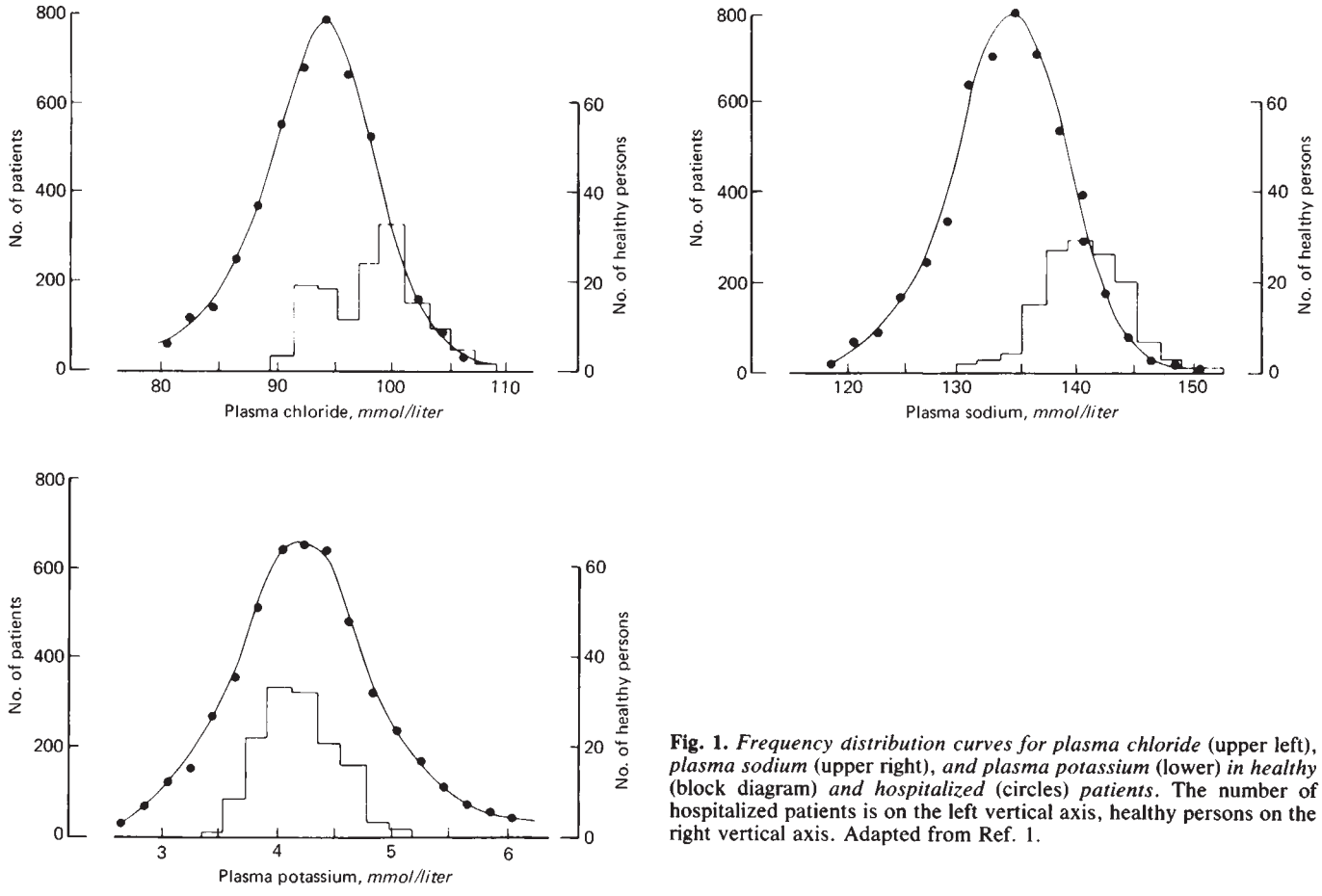

Fig. 1. *Frequency distribution curves for plasma chloride* (upper left), *plasma sodium* (upper right), *and plasma potassium* (lower) *in healthy* (block diagram) *and hospitalized* (circles) *patients.* The number of hospitalized patients is on the left vertical axis, healthy persons on the right vertical axis. Adapted from Ref. 1.

tion, I wish to emphasize in this discussion the mechanisms that lead to this common electrolyte disturbance. I also plan to discuss the clinical settings in which hospital-associated hyponatremia occurs and the management and outcome of patients who develop it.

Pathophysiologic considerations

All cells actively extrude sodium ions from their interior, and their low permeability to sodium limits its passive re-entry. Thus sodium and its accompanying anions are the major extracellular solutes, with glucose, urea, and other ions contributing to a lesser degree. As a corollary, sodium and its accompanying anions are the main determinant of plasma osmolality. Because virtually all body water is in osmotic equilibrium, an acute lowering of the plasma sodium concentration due to relative water excess leads to an osmotic gradient and to a movement of water from the extracellular to intracellular compartments [6]. The resultant cerebral edema coupled with the brain's rigid encasement can lead to significant neurologic symptoms and morbidity [3–6].

Many years ago Edelman and associates found that the serum sodium concentration depended on the following relationship [7]:

$$\text{Serum sodium} = \frac{\text{Total body sodium} + \text{total body potassium}}{\text{Total body water}}$$

Thus, as every medical student recognizes, the plasma concentration of sodium reflects the prevailing *relationship* between solute and water balance and not the *absolute amount* of either solute or water present in the body. The absolute amounts of sodium and water do determine the extracellular fluid volume. In my experience, a reduction in plasma sodium concentration in hospitalized patients is most often due to an increase in total body water. Such an increase implies continued water intake in the presence of a decreased capacity for water elimination.

Appropriate elimination of ingested water is, of course, the consequence of the kidney's normal response to suppressed arginine vasopressin (AVP). Ingestion of a water load directly reduces plasma osmolality; hypoosmolality in turn suppresses hypothalamic synthesis and posterior pituitary release of AVP [8]. Arginine vasopressin normally increases the permeability of the apical surface of renal collecting tubular epithelial cells to water. In the presence of a hypertonic interstitial environment surrounding the collecting duct, the increase in water permeability induced by AVP results in renal water retention. Suppression of AVP by hypoosmolality allows excretion of the water load. However, a large body of experimental evidence has shown conclusively that continued secretion of vasopressin can occur despite hypoosmolality, thus establishing the existence of so-called nonosmotic stimuli for vasopressin secretion [8]. Examples of clinical conditions associated with such stimuli include cardiovascular instability, edematous and volume-

depleted states, glucocorticoid deficiency, hypothyroidism, derangements of arterial blood gases, the postoperative state, and certain malignancies [2, 5, 9–15].

We recently studied the circulating levels of several hormones in 72 patients with hospital-associated hyponatremia; we were especially interested in the possible pathogenetic role of AVP in this disorder [2]. We detected AVP in the plasma of 71 of 72 hyponatremic patients. The majority of patients with hospital-associated hyponatremia were receiving hypotonic fluid intravenously [2]. The combination of high plasma AVP and hypotonic fluid administration leads to water retention and to hyponatremia.

In an effort to determine the cause of the nonosmotic secretion of AVP in these patients, we measured plasma concentrations of renin activity, norepinephrine, and aldosterone. In patients with edema or hypovolemia, measurements of mean arterial blood pressure (low), pulse rate (high), and of plasma norepinephrine, aldosterone, and renin activity (all of which are increased) suggest baroreceptor-mediated, nonosmotic release of AVP [2]. However, many of the patients we studied and the patients under discussion today had no evidence of volume depletion or cardiovascular instability and normal plasma concentrations of renin activity and aldosterone. Thus, the cause of the nonosmotic release of AVP in these patients remains unknown.

For a water load to be excreted normally, other aspects of renal function in addition to ADH-responsiveness must be operating properly. For example, normal rates of glomerular filtration and proximal tubular reabsorption are necessary to deliver a sufficient quantity of tubular fluid to the distal nephron. Thus, as is well known, excessive water intake in the presence of renal failure leads to water retention, positive water balance, and hyponatremia. It is possible that increased proximal reabsorption accounts for some of the impairment of renal diluting capacity in certain edematous patients [8].

In summary, hospital-associated hyponatremia is often due to an increase in body water relative to the major extracellular fluid body solute, sodium. Thus hyponatremia can occur in the presence of either normal, decreased, or increased total body serum. This increase in body water is often encountered in clinically normovolemic patients and is caused by the intravenous administration of hypotonic fluid to patients unable to excrete water normally because of a nonosmotic stimulus to AVP secretion.

Clinical approach

A comparison of some of the findings from two surveys of hospital-associated hyponatremia is presented in Table 1. Hyponatremia, as it is currently encountered, is often a hospital-acquired disorder occurring in elderly patients with severe underlying disease [2, 15]. Table 2 details the clinical setting in which hyponatremia occurred in 194 patients we studied prospectively. In 30% of the patients, hyponatremia could be attributed either to hyperglycemia, to severe renal failure (and free water administration), or to laboratory error. Thus, these three possibilities should be considered early in the diagnostic evaluation of the hyponatremic patient.

The remaining 70% of hyponatremic patients included in Table 2 were classified according to clinical assessment of extracellular fluid volume, as is common in clinical practice

Table 1. Hyponatremia in hospitalized patients

	Baran et al [2][a]	Anderson et al [15][a]
	(n = 78)	(n = 194)
Definition (*mEq/liter*)	<128	<130
Percentage of males	49	50
Mean age (*years*)	65	58
Mortality (%)	27	11
Hospital acquired (%)	67	67

[a] Numbers in brackets refer to reference.

Table 2. Clinical setting of hyponatremia among inpatients at the University of Colorado Hospital[a]

Setting	Percentage
Normovolemia	34
Hypovolemia	19
Edema	17
Hyperglycemia	16
Renal failure	9
Laboratory error[b]	5

[a] Data are from Ref. 2.
[b] All patients had confirmatory studies.

[16–19]. Hyponatremia occurring in patients with an edematous disorder (28 with cardiac failure, 6 with liver disease, and 4 with hypoalbuminemia without liver disease) was seen in 19.4%. Hypovolemic disorders (9 patients with gastrointestinal losses, 8 with diuretic use, 7 with combined gastrointestinal losses and diuretic use, 4 in the postoperative state, and 5 with miscellaneous conditions) accounted for 16.8% of hyponatremia. The clinical setting of the 34% of hyponatremic patients who were normovolemic included the immediate postoperative period (0 to 72 hours) (20 patients), active intracranial disease (11 patients), disseminated cancer (11 patients), administration of pharmacologic agents known to impair renal water excretion (6 patients), massive (>12 liters) fluid resuscitation therapy for extensive burns (3 patients), pneumonia (3 patients), more than one of the above conditions (8 patients), and miscellaneous conditions (4 patients). The 66 normovolemic patients (mean urinary sodium concentration, 71 + 3.8 mEq/liter) comprised the largest single group. By conventional criteria [21–23] most of these normovolemic patients would be diagnosed as having the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Within barely 25 years of first being described, this syndrome has become the most commonly recognized cause of hyponatremia among hospitalized patients [21]. Dr. Martinez-Maldonado presented an excellent discussion of SIADH in another Nephrology Forum [23]. Today I would like to focus on hyponatremia in patients with pulmonary disorders and in those in the postoperative state, because these two circumstances are encountered so frequently in hospitalized patients and because the hyponatremia is usually normovolemic.

The first patient presented today appears to have SIADH associated with intrathoracic disease that had resulted from complications of cystic fibrosis. A number of pulmonary processes have been reported to cause SIADH (Table 3). The underlying mechanisms whereby intrathoracic disease processes lead to nonosmotic release of AVP are not clearly under-

Table 3. Pulmonary disorders associated with hyponatremia[a]

Acute respiratory failure
Severe chronic obstructive pulmonary disease
Acute bronchial asthma
Prolonged mechanical ventilation
Intrathoracic infectious processes
Intrathoracic neoplasms

[a] Data are from Ref. 12.

Table 4. Mechanisms underlying nonosmotic secretion of AVP in pulmonary disorders[a]

Hypoxemia and hypercapnic acidosis
Hemodynamic abnormalities
Unregulated synthesis and release of AVP by the tumor
Pharmacologic agents
Stress

[a] Data are from Ref. 12.

stood. Possible mechanisms are listed in Table 4. Experimental and clinical studies indicate that hypoxemia as well as hypercapnia can cause release of AVP [11–14, 24, 25]. For example, in the conscious dog, both hypoxemia and hypercapnic acidosis increase plasma AVP without producing an increase in plasma osmolality. Combined hypoxemia and hypercapnic acidosis markedly increase plasma AVP (Fig. 2). In the clinical setting, abrupt decreases in PO_2 and increases in PCO_2 also are often associated with AVP release [11]. We have found marked increases in plasma AVP in hypoxemic and hypercapnic patients with acute respiratory failure (Fig. 3). These elevated AVP levels slowly returned towards normal with improvement in hypoxemia and hypercapnia.

It is also likely that hemodynamic abnormalities contribute to release of AVP in some patients with pulmonary diseases. For example, hypoxemia and hypercapnic acidosis lower peripheral vascular resistance [13, 14]. Concomitant cardiac failure frequently is present in patients with severe lung disease and can, by hemodynamic mechanisms, lead to AVP release [9].

Mechanical ventilation is one clinical setting in which hemodynamic alterations appear to play a key role in nonosmotic release of AVP. Retrospective clinical observations by Sladen et al in 1968 first suggested that mechanical ventilation can result in renal water retention [26]. In these studies, 19 of 100 patients requiring prolonged mechanical ventilation developed water retention. None of the patients had clinical evidence of cardiac failure, but 11 of 19 had evidence of pulmonary edema on chest x-ray. A significant increase in body weight (2.6 kg) due to positive water balance (3.8 liters) and a decrease in hematocrit and plasma sodium concentration (-5.8 mEq/liter) were noted. With water restriction and diuretic therapy, body weight and plasma sodium concentration returned to baseline levels and pulmonary edema resolved.

Recent studies in anesthetized dogs have uncovered mechanisms that may explain the stimulation of AVP induced by positive end-expiratory pressure (PEEP) ventilation [27]. In these studies both 10 and 15 cm H_2O PEEP increased plasma AVP and decreased mean arterial pressure and cardiac output. The ability of PEEP to increase AVP was partially attenuated by three maneuvers: plasma volume expansion (which dampened the hemodynamic effects of PEEP), cervical baroreceptor denervation, and normalization of the associated increase in intracranial pressure [27]. The combination of baroreceptor denervation and control of intracranial pressure nearly abolished the PEEP-induced increase in AVP. These observations suggest that the central hemodynamic effects plus the associated increase in intracranial pressure are major factors underlying AVP release during PEEP ventilation.

Although an association of intrathoracic infections and neoplastic processes with hyponatremia has been known for several years, the mechanism(s) responsible for this form of hyponatremia are not clearly established [28, 29]. Amatruda and coworkers suggested in 1963 that ectopic AVP production might account for SIADH associated with lung neoplasms [30]. These authors were able to find AVP-like bioactivity in tumor extracts. Substantial data suggest that bronchogenic carcinomas, particularly of the "oat cell" type, are capable of unregulated synthesis and release of AVP. These observations include: failure of centrally acting inhibitors of ADH release (for example, alcohol, hydantoin) to ameliorate the syndrome; the presence of ADH-like activity by bioassay and radioimmunoassay in tumor extracts and plasma; the incorporation of radioactive phenylalanine by tumor slices in vitro into the same chromatographic peak with AVP; electron microscopic evidence of secretory granules in tumor specimens from patients with the syndrome; identification of neurophysins (carrier proteins of AVP) in tumor specimens; and resolution of the syndrome after surgical removal of the tumor [12, 30–32].

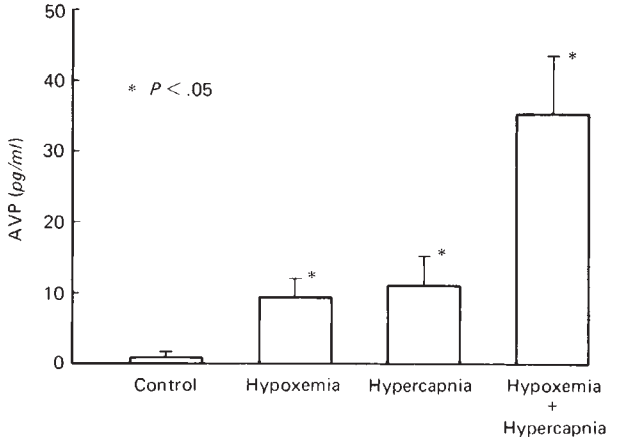

Fig. 2. *Effect of hypoxemia and hypercapnia on plasma arginine vasopressin* (AVP) *in conscious dogs.* Adapted from Ref. 13.

Whereas bronchogenic carcinomas clearly can synthesize AVP, the mechanism of AVP secretion associated with intrathoracic infectious processes is less apparent. The association between tuberculosis and hyponatremia has been known for years [28, 29, 33, 34]. Several investigators have demonstrated intact adrenal and renal function as well as the absence of volume depletion in hyponatremic patients with tuberculosis [29, 33]. Shalhoub and Antoniou suggested that unregulated neurohypophyseal release of ADH might account for the hyponatremia in patients with tuberculosis [33]. Water-loading tests performed on 6 patients with hyponatremia and tuberculosis demonstrated decreased renal water excretion in 5. This

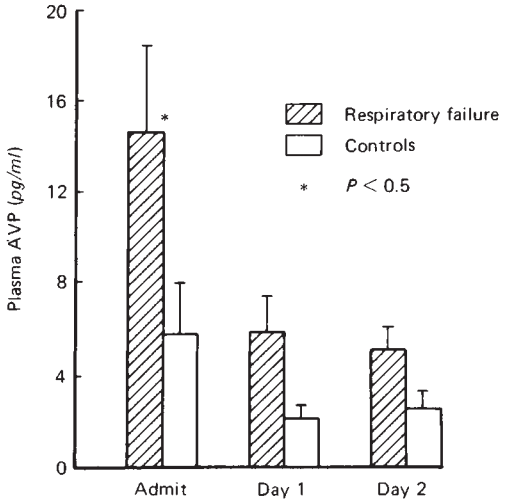

Fig. 3. *Effect of acute respiratory failure on plasma arginine vasopressin* (AVP) *in patients with acute respiratory failure* (hatched bars) *and patients admitted with chest pain* (open bars).

abnormal response was abrogated or improved in all after ethanol administration [33]. Vorherr et al demonstrated antidiuretic activity in involved lung tissue and in urine in a patient with far-advanced tuberculosis [34]. By bioassay, antidiuretic activity was highest in the active inflammatory zone, lower in the central caseous zone, and absent in uninvolved tissue [34]. Neither a suspension of *Mycobacterium tuberculosis* nor culture media containing its metabolites demonstrated any antidiuretic bioactivity. These investigators postulated that pulmonary tuberculous lesions may synthesize and liberate ADH in a fashion similar to that occurring in bronchogenic carcinoma, although passive adsorption of AVP was not ruled out. No further examination of this hypothesis has been published.

As in the patient under discussion, SIADH also has been documented in a variety of nontuberculous pulmonary infections. Thus, cavitary aspergillosis, acute bacterial and viral (adenovirus 7 and 12) pneumonias, and chronic infectious pneumonitis all have been associated with SIADH [35]. The precise mechanism of AVP secretion in nontuberculous pulmonary infections remains to be clarified. In summary, factors that might have contributed to stimulation of AVP in the first patient discussed include hypoxemia, pulmonary infection, hemodynamic abnormalities, and possibly pharmacologic agents and stress.

The second patient developed hyponatremia in the immediate postoperative state. A recent prospective study demonstrated that 25% of hospital-acquired hyponatremia occurred during the postoperative period [2, 15]. A minimal estimate of the frequency of postoperative hyponatremia was 4.4% of 1088 consecutive operative procedures [15]. Other reports suggest an even higher frequency (Table 5) [36–50].

What is the pathogenesis of postoperative hyponatremia? The postoperative state long has been known to be characterized by avid renal sodium and water retention [40, 41, 44–46]. Release of AVP from the posterior pituitary appears to be partly responsible for the renal water retention. Bioassay and radioimmunoassay results demonstrate high plasma AVP concentrations following anesthesia and surgery [15, 44–53]. Although the

Table 5. Frequency of postoperative hyponatremia[a]

Procedure	Percentage
Cardiovascular	20–30
Gastrointestinal	20–60
Spinal fusion	20
T-tube drainage	22
Mitral valve surgery	30
General surgery/trauma	40
Subtotal gastrectomy	67

[a] Data are from Refs. 15, 36–53.

increase in plasma AVP usually subsides about 72 hours after operation [8], it can persist for up to 5 days [50]. The precise mechanism whereby the operative state leads to secretion of AVP has not been ascertained.

In the presence of circulating AVP, administration of hypotonic fluid and rarely isotonic fluid (if urinary osmolality is very high) results in renal water retention and hyponatremia [54]. Indeed, 94% of postoperative hyponatremic patients in a recent study were receiving hypotonic fluids at the time hyponatremia developed [15]; this observation has been confirmed by others [36, 39, 40, 48, 53, 55]. In two previous studies in which the daily postoperative requirement for electrolyte was given in either an isotonic or hypotonic solution, hyponatremia occurred only in patients receiving hypotonic fluids [36, 52].

What are the consequences of postoperative hyponatremia? None of the postoperative patients with mild hyponatremia (serum sodium, 128 mEq/liter) in a recent prospective study developed clinically obvious neurologic deterioration concomitant with the onset of hyponatremia [15]. Another report demonstrated the occasional development of severe neurologic dysfunction and death in some patients with severe postoperative hyponatremia, however (serum sodium <110 mEq/liter) [5]. Finally, in edematous postoperative patients, the observed water retention was associated with increasing pulmonary capillary wedge pressure and radiographic evidence of pulmonary vascular congestion [15].

Outcome determinants in patients with hyponatremia

I would now like to discuss the association between hyponatremia and poor clinical outcomes. Hyponatremia did not appear to be associated with a poor outcome in either of the patients discussed today. Figure 4 demonstrates, however, that hyponatremia is a marker for poor outcome in several disease states [56–59]. Substantial evidence suggests that mild hyponatremia, as in the 2 patients discussed, usually is asymptomatic and is associated with little increase in morbidity or mortality [2, 16]. In fact, more severe hyponatremia probably is associated with a high mortality rate merely because it is an accompaniment of severe underlying disease. Many patients with hyponatremia are extremely sick with advanced heart, liver, or lung disease or with cancer [2, 3, 16]. Flear and Hilton have demonstrated that the likelihood of developing hyponatremia after myocardial infarction is a direct function of the extent and complications of the infarction [56]. Hyponatremia is rare with mild heart failure but more common with increasingly severe cardiac dysfunction. In other clinical settings, such as tuberculosis and childhood diarrhea in the third world, hyponatremia is more likely to occur in patients with underlying malnutrition

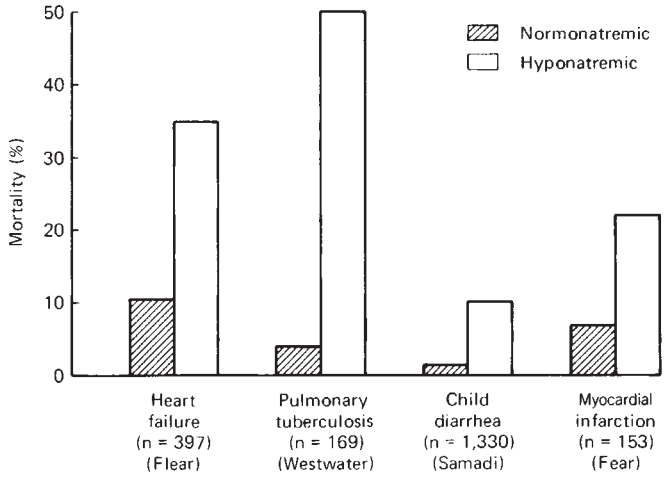

Fig. 4. *Mortality rates in normonatremic* (hatched bars) *and hyponatremic* (open bars) *patients with a variety of illnesses.*

[58, 59]. Thus the consistently higher mortality in hyponatremic than in normonatremic patients likely reflects the nature and severity of the underlying disease process (Table 1, Fig. 4) [2, 3, 16, 55–59].

One determinant of morbidity in hyponatremic patients is the rate of decline of the plasma sodium concentration [6]. Experimental studies clearly indicate that the severity of symptoms and the degree of cerebral edema are directly related to the speed with which hyponatremia occurs [6]. In two prospective studies, the frequency with which severe hyponatremia was thought to cause significant central nervous system symptoms was 3% and 15%, respectively, of all patients with hyponatremia [2, 16]. A number of clinical observations amply document that severe morbidity and mortality accompany acute, severe hyponatremia [4–6]. A relationship between the magnitude of decline in plasma sodium concentration and outcome also has been suggested. Thus mortality rates appear to be one- to threefold higher when the serum sodium concentration is less than 120 mEq/liter [2, 16].

In explaining the outcome of patients with hyponatremia, one must also take cognizance of the threapy used in this disorder. Correction of mild, asymptomatic hyponatremia (usually >120 mEq/liter) requires only water restriction and treatment of the primary disorder [60].

If water restriction is unsuccessful, demeclocycline has become the preferred therapy for chronic inappropriate secretion of antidiuretic hormone. In 1978, Forrest et al reported that demeclocycline was superior to lithium in the treatment of chronic SIADH [61]. After 5 to 14 days of 600 to 1200 mg/day of demeclocycline, mean serum sodium concentration increased from 122 + 4 to 139 + 1 mEq/liter in 10 patients with unrestricted water intake. In 3 patients, lithium therapy was unsuccessful and led to central nervous system side effects in 2. Several other therapeutic agents including urea, phenytoin, and furosemide have been advocated as therapeutic agents in SIADH [62–64]. None of these approaches has been demonstrated to be superior to demeclocycline. Moreover, in compliant patients, water restriction remains the cornerstone of therapy.

The recent discovery of vasopressin antagonists by Manning and Sawyer has opened new directions for the therapy of hyponatremia associated with excess vasopressin [65]. Experimental studies show that these vasopressin analogues inhibit stimulation of adenylate cyclase activity by vasopressin in isolated rat nephron segments including collecting tubules and medullary thick ascending limbs of Henle [66]. The vasopressin antagonists do not block the stimulatory effect of parathyroid hormone or calcitonin on adenylate cyclase activity in the appropriate nephron segments [66]. The vasopressin antagonists also inhibit vasopressin-stimulated hydraulic conductivity in perfused rabbit cortical collecting tubules [66]. Finally, these agents have been shown to reverse the pathologic water retention that occurs in glucocorticoid and mineralocorticoid deficiency [67]. Thus these agents ultimately might prove to be of therapeutic benefit in selected hyponatremic states. To date, no information on the use of these agents in clinical disorders that are characterized by water retention is available.

Treatment of severe, symptomatic hyponatremia is controversial. If left untreated, either death or severe neurologic disability can result [4–6]. Unfortunately, treatment itself can produce serious disability. Recent experimental and clinical observations have been interpreted as suggesting that rapid correction of hyponatremia, especially chronic hyponatremia, can lead to central pontine myelinolysis [68–75]. This syndrome, a demyelinating disease of the pons, is associated with a variety of neurologic symptoms. It occurs in patients with alcoholism, malnutrition, and other debilitating diseases [71, 72]. The possible relationship between central pontine myelinolysis and correction of hyponatremia was reviewed by Ayus et al [3]. In the absence of overcorrection to frank hypernatremia I do not believe that a convincing case has been made for this association. Several observations argue against the existence of a clearcut relationship between rapid correction of hyponatremia and central pontine myelinolysis: (*1*) Most of the reported patients with central pontine myelinolysis were not hyponatremic [3, 72, 73]; many, in fact, were hypernatremic [72]; (*2*) Less than 5% of patients with central pontine myelinolysis had a history of rapid correction of hyponatremia [3, 71, 76]; (*3*) In the few instances in which central pontine myelinolysis was attributed to rapid correction of hyponatremia, rapid correction of hyponatremia was not documented in some, and in the others the patients were made frankly hypernatremic [3, 70]; (*4*) In experimental studies of hyponatremic rats in which rapid correction of hyponatremia was associated with central pontine myelinolysis, it is likely that overcorrection to frank hypernatremia also occurred [69]; more recent experimental studies in the rat demonstrate that rapid correction of hyponatremia with hypertonic saline to mildly hyponatremic levels does not cause significant brain lesions [76]; (*5*) Retrospective analysis reveals that rapid correction of severely symptomatic, acute hyponatremia is associated with a lower mortality rate than is slow correction [3, 77]; and (*6*) Recent clinical reports, albeit involving small numbers of patients, suggest that rapid correction of severe hyponatremia to slightly hyponatremic levels does not produce central pontine myelinolysis [78, 79]. Thus, in severe hyponatremic emergencies, it is unlikely that rapid correction, that is, correction sufficient to cause serum sodium to rise by approximately 1.5 mEq/liter/hour to mildly hyponatremic levels, approximately 125 mEq/liter, leads to central pontine myelinolysis.

Specifically, in normovolemic patients either thought to be symptomatic from hyponatremia or with marked hyponatremia (<110 mEq/liter), I advocate the use of furosemide (1 mg/kg body weight) and replacement of urinary losses with 3% NaCl to elevate the serum sodium concentration to about 125 mEq/liter [79].

In summary, the nature and severity of the underlying disease state and of the magnitude and speed of decline of plasma sodium concentration appear to be the major determinants of the outcome in hyponatremic patients. In the occasional patient with severe, symptomatic hyponatremia, rapid correction to a plasma sodium concentration of about 125 mEq/liter appears to be safe.

Questions and answers

DR. DAVID BUSHINSKY (*Renal Section, Mitchell Hospital, Chicago*): Some hormones, such as parathyroid hormone, are secreted at a basal level whether or not there is any stimulus for secretion [80]. Is vasopressin secreted in the this manner? If so, could unregulated basal secretion explain some of what we think of as SIADH?

DR. ANDERSON: As I noted previously, there are two main stimuli for vasopressin release. Increasing osmolality is one. Gary Robertson has shown that, as osmolality increases, vasopressin release begins to occur at a certain "threshold" osmolality value [81]. This threshold value is determined by multiple factors including age, sex, genetic variables, and perhaps central hemodynamic status. Typically, the relationship between increased osmolality and increased vasopressin release is linear and very steep, small increases in osmolality producing appreciable increases in vaspressin. The relationship between the strength of nonosmotic stimuli and vasopressin release is quite different. For example, as much as a 10% to 15% decrease in extracellular fluid volume may be required to initiate vasopressin release [81]. Moreover, the increase in plasma vasopressin with nonosmotic stimuli is logarithmic rather than linear. Thus whether there is "basal" secretion of vasopressin greatly depends on the state of water balance and basal plasma osmolality.

DR. MARSHALL LINDHEIMER (*Renal Section, Mitchell Hospital, Chicago*): If there is a "tonic" secretion of vasopressin, the hormone circulates at a level that is too low to affect urinary concentration; thus, in a sense there is a certain osmotic "set point" at which secretion is "turned off" appropriately. Some investigators claim that vasopressin can be measured at levels too low to affect urinary osmolality (that is, the urine remains maximally dilute). Others find it unmeasurable at those levels.

DR. JORDAN J. COHEN: You have emphasized appropriately the dominant role that ADH plays in the pathogenesis of clinically occurring hyponatremia. But it is also well established that appreciable urinary concentration can occur in the total absence of ADH; I believe Berliner and Davidson were the first to demonstrate that reduced GFR or, by implication, increased proximal sodium reabsorption, could result in water retention by the kidney. Many of the clinical circumstances in which hyponatremia occurs are characterized by avid proximal sodium reabsorption, often in association with some reduction in GFR. What is your current view about the relative role of these physiologic abnormalities in the pathogenesis of hyponatremia?

DR. ANDERSON: It is my bias that ADH plays the major role even through reduced distal delivery may contribute. Studies in animal models of heart failure and liver disease show that removal of the source of ADH by hypophysectomy corrects the diluting defect by 95% [82, 83]. I think a clear-cut answer to your question will likely be provided by studies with the newly available, specific vasopressin antagonists.

DR. BUSHINSKY: In chronic hypernatremia, it appears that idiogenic osmoles form in the brain and that this process protects neurons against volume changes [84]. Is there any evidence that chronic hyponatremia causes neurons to decrease their effective osmolality?

DR. ANDERSON: Current concepts of cell volume regulation suggest that many cells respond to osmotic challenge by first exhibiting osmometric behavior followed by a regulatory volume adjustment [85]. The regulatory volume adjustment phase involves enhanced cell solute exit and decreased cell solute entry sufficient to return cell volume to normal [85]. Some experimental evidence suggests that volume readjustment in the brain occurs in chronic hyponatremia [6].

DR. COHEN: We know that in some circumstances serum sodium can fall by 30% or more. If there were not a substantial fall in the effective osmolality within the cell, one would have to envision a proportionate increase in the volume of the brain; obviously a change of that magnitude is impossible. Unless one believes there is a barrier to water movement into brain tissue, there must be some alteration in the osmotic activity of the intracellular enviroment. Do you agree?

DR. ANDERSON: Your point has been brought up with regard to SIADH. The initial observations by Schwartz and Bartter suggested that hyponatremia could not be explained by the positive water balance or the loss of salt, and they postulated that there was inactivation of intracellular solutes. Either inactivation of intracellular solutes or negative cell solute balance (that is, cellular solute efflux greater than influx) would be necessary to autoregulate cell volume toward normal. In studies that we have performed in an experimental model of SIADH, however, hyponatremia can be accounted for totally by positive water and negative solute balances [54].

DR. JAMES BOURDEAU (*Renal Division, Michael Reese Hospital*): Work done by Grantham et al in isolated rabbit kidney tubules [86] and by Kregenow and coworkers in duck erythrocytes [87] investigating the volume response to hypotonic challenge showed that potassium chloride appears to leave these cells. The mechanism causing potassium chloride to exit from mammalian cells might vary depending on the system, but loss of these solutes appears to be one of the protective mechanisms for minimizing cellular swelling in response to a sudden hypoosmotic stress.

DR. ARNOLD BERNS (*Staff Nephrologist, Michael Reese Hospital*): As you pointed out, the vast majority of hyponatremic patients have an elevated AVP level. How do you categorize the ones who don't? Occasionally we see a hyponatremic patient with maximally dilute urine. Such patients usually have a high urine flow and they improve rapidly, usually within the first 24 hours. I'm not sure how to explain this, but I have always wondered whether the rate of water intake might transiently exceed maximal free-water clearance. If so, it might be possible to get a transient but significant dilutional hyponatremia in the absence of renal disease and without secretion of antidiuretic hormone. Do you think this actually happens?

DR. ANDERSON: Yes. First, what is going on in hyponatremic patients who don't have measurable ADH? The ADH assay is difficult, and only 1.0 pg/ml increases urinary osmolality by 250 mOsm/kg H_2O. The traditional explanation has been that AVP is difficult to measure in the very low range. There might be other explanations for persistent hypoosmolality with very low ADH levels as well. There may be an entity of reset osmostat in which, for example, one regulates around a plasma osmolality of 275 mOsm/kg H_2O. There is some evidence that this might happen in pregnancy. Second, the diluting capacity can be overwhelmed if one drinks a great deal of water in a hurry. This happens predominantly in psychotic patients. We have seen instances in which patients took a hose attached to the tap and put it down their stomach. Although you or I can get rid of 20 or 25 liters of water in a day, we can't get rid of large quantities in one or two hours. There is no doubt that, acutely, our renal diluting capacity can be overwhelmed.

DR. SERAFINO GARELLA (*Department of Medicine, Michael Reese Hospital*): I believe that those patients who develop hyponatremia because of excessive water intake of a magnitude sufficient to outstrip their normal diluting capacity can be distinguished on clinical grounds because they have a large output of maximally dilute urine. This finding should markedly simplify the differential diagnosis.

DR. COHEN: Another setting in which transient, non-ADH-mediated water retention might occur is in individuals who are ingesting very low solute loads, especially when the minimum urinary osmolality that can be achieved is a little higher than normal. For example, the elderly patient who is subsisting on a tea-and-toast diet and who has a slight intrinsic impairment in diluting capacity might be unable to excrete ordinary amounts of ingested water fast enough to avoid hyponatremia. Would you agree with that?

DR. ANDERSON: Yes.

DR. LINDHEIMER: Concerning the ability of an individual to maintain a chronic hyponatremic state in the absence of vasopressin: I'm aware of one circumstance in animals in which this occurs. Some years ago we studied gestation in Brattleboro rats with hereditary diabetes insipidus, a strain in which the homozygous animals produce no vasopressin. We observed that the osmotic threshold for drinking was descreased during gestation in these animals and that the gravid homozygous animal was able to maintain its plasma osmolality at approximately 10 mOsm/kg below nongravid levels throughout the gestation. Thus the assertion that individuals with normal renal function cannot drink enough to maintain a chronically hypoosmotic state might not be valid.

DR. GARELLA: What are your thoughts regarding two conditions in which, to my knowledge, hyponatremia has not been reported to be associated with increased AVP levels, namely, the so-called "cerebral salt wasting" syndrome, and the hyponatremia that is occasionally seen following the use of thiazide diuretics, and which has been attributed to potassium depletion?

DR. ANDERSON: I have to confess that I haven't studied the issue of cerebral salt wasting very much so I can't answer your question. But I would like to dispute the notion that patients with SIADH are "salt wasters." Schwartz and Bartter described their patients as having renal salt-wasting. I don't think that is a totally accurate characterization. In the steady state, patients with SIADH put out as much salt in the urine as they take in. Moreover, from a physiologic perspective, SIADH is a modestly volume-expanded state. In the setting of SIADH and positive water balance, some of the retained water remains in the extracellular fluid. Thus, the GFR is high, and cardiac output can be on the high side. In that setting with a high filtered load of sodium, decreased proximal reabsorption, and variable aldosterone secretion (both low and high values have been reported), I think that salt in the urine reflects sodium intake. A number of years ago Nolph and Schrier demonstrated that a patient with well-documented SIADH who had a very low sodium intake could reduce urine sodium excretion to negligible levels [88]. Thus although we traditionally talk about SIADH, particularly SIADH associated with intracranial pathology, like cerebral salt wasting, I think that patients with these disorders excrete urinary sodium equivalent to their sodium intake.

The second question brought up by Dr. Garella is a more problematic area, that is, the pathogenesis of hyponatremia that occurs in the potassium-depleted patient. These patients are almost invariably taking thiazide diuretics [89]. In patients taking thiazides, it traditionally has been thought that natriuresis leads to modest volume depletion; the volume depletion in turn stimulates ADH secretion, and following ingestion of a lot of water, hyponatremia results. A recent study of thiazide-induced hyponatremia demonstrated that urinary concentration of sodium and potassium exceed 150 mEq/liter, whereas the serum values of these electrolytes were less than 110 mEq/liter [90]. Thus thiazides can potentially induce hyponatremia without producing changes in water balance. The observation has been made repetitively that many patients with thiazide-induced hyponatremia have marked hypokalemia and, in selected circumstances, restore their plasma sodium to normal with potassium repletion alone [91]. Fichman et al postulated that hypokalemia or potassium depletion somehow lowers the osmotic or nonosmotic threshold for release of vasopressin. No data are available to support this contention as far as I can tell. Another possible explanation is that as one becomes potassium depleted, potassium shifts from intracellular to extracellular sites. Concomitantly, sodium and hydrogen ions go inside the cell and are relatively inactive as intracellular solutes. This is an area that is poorly understood.

DR. COHEN: Dr. Anderson, in your opinion does chronic, asymptomatic hyponatremia result in any adverse consequences?

DR. ANDERSON: If you are talking about a sodium concentration in the 125 to 130 mEq/liter range that has developed slowly, I don't think there is much morbidity or mortality from the hyponatremia by itself.

DR. GARY TOBACK (*Renal Section, Mitchell Hospital*): You indicated that the plasma AVP concentration is often strikingly elevated during the intra- and postoperative periods, and can remain so for at least a day or two after surgery. Three questions spring to mind. First, why don't these patients routinely manifest the pressor effects of AVP when such high concentrations are present in the plasma? Second, surgeons commonly administer large amounts of hypotonic fluids in the postoperative period, so why is the frequency of hyponatremia only 4.5% or so? Third, what counterregulatory mechanisms blunt these expected pressor and antidiuretic effects of the hormone when it is present at such a high concentration for a prolonged period?

DR. ANDERSON: With regard to the frequency of the develop-

ment of hyponatremia, we studied only patients whose serum sodium level was less than 130 mEq/liter. In our hospital, a normal value is about 141 ± 1 mEq/liter. If we included all sodium values less than 138 mEq/liter, we would have a much higher incidence of postoperative hyponatremia. With regard to hypertension, AVP levels of 20 to 30 pg/ml might be required to consistently exert a vasoconstrictor effect, and those levels are not seen in these patients. The factors that counteract the vasoconstrictor effects of vasopressin are not well established, but might include prostacyclin and the kinins.

DR. LINDHEIMER: Do you think that AVP is the only humoral agent responsible for urinary concentration? I ask this question because those of us who use radioimmunoassays to measure this hormone occasionally encounter individuals who concentrate their urine, but whose AVP levels are below the limits of detection of our assay. Such observations suggest that the AVP molecule in some individuals might be altered and not recognized by the antiserum. One might also speculate that in some physiologic or pathophysiologic states there are circulating substances capable of stimulating adenyl cyclase production in critical areas of the nephron. What is your opinion of that?

DR. ANDERSON: I agree that some day we might identify another antidiuretic hormone, or at least systems that modify antidiuretic hormone. For example, in the isolated perfused cortical collecting tubule, atrial natriuretic factor is an inhibitor of vasopressin. I think there are a lot of substances such as adenosine, prostaglandins, atrial natriuretic factor, and the kinins that influence cellular regulation of vasopressin action. I wouldn't rule out an as-of-yet unidentified substance that also contributes to urine concentrating ability.

DR. FREDRIC COE (*Renal Section, Mitchell Hospital*): The message I take home is that water elimination is diminished in hospitalized patients because vasopressin is often elevated, albeit by a number of factors. Thus, virtually all serious hyponatremia in hospitalized patients is iatrogenic. So if we simply improve the way in which we administer water, the whole problem should disappear. It seems to me from what you've said that better education is the best treatment for hospital-acquired hyponatremia.

DR. ANDERSON: That is precisely the message I intended to deliver. Hyponatremia is often iatrogenic and is preventable. Recall that in two large prospective studies hyponatremia was hospital-acquired in 67% of cases [2, 16].

DR. KAI LAU (*Renal Division, Michael Reese Hospital*): You have shared with us some recent observations from which you concluded that chronic exposure to vasopressin can desensitize the collecting tubule cell to its action. How would you extrapolate this observation to the patient with SIADH in whom ADH levels are persistently high?

DR. ANDERSON: We recently have generated data in cultured collecting tubular cells that demonstrate that chronic exposure to vasopressin densensitizes these cells [91]. Thus if you expose the collecting tubular cells in culture to vasopressin for one hour, wash them, and rechallenge them with vasopressin, you will see a marked decrease in adenylate cyclase activity [91]. This densensitization can be prevented by pertussis toxin, so we believe that the inhibitory guanine nucleotide regulatory protein might play a role in this desensitization.

DR. COHEN: Could you clarify an issue that has always puzzled me about chronic hyponatremia in patients with SIADH? It is well established that ADH administered chronically to an animal with a fixed water intake causes maximal water retention only over the first few days. Thereafter, urine becomes less concentrated and hyponatremia is at least partially repaired. In other words, the animal "escapes" from the action of ADH in much the same way that animals escape from the effects of DOCA. I would be interested, first of all, in your ideas about the mechanism of the ADH-escape phenomenon and, second, in why we don't observe such escape in the clinical setting.

DR. ANDERSON: If you expose an animal to high concentrations of vasopressin and a fixed intake of free water, renal water retention occurs and hyponatremia develops. However, a new steady state is ultimately reached during which plasma sodium remains constant and renal excretion of all ingested water occurs [54]. Thus, after a period of water retention, escape from the hydroosmotic effect of vasopressin can be documented. It is clear that this phenomenon can only occur in the presence of positive water balance [54, 92]. The precise mechanisms of escape from vasopressin are not clear. However, I think that prostaglandin E_2 contributes to the escape [54]. In addition, plasma volume expansion as well as an increase in cardiac index, plasma volume, renal blood flow, and glomerular filtration rate all accompany the escape phenomenon and can contribute to its generation [54].

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